POINTS IN THE PHARMACOLOGY OF CERTAIN DRUGS USED FOR STOMACH EFFECTS.[1]

By W. A. Bastedo, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, COLUMBIA UNIVERSITY; ATTENDING PHYSICIAN, CITY HOSPITAL, NEW YORK; ASSOCIATE ATTENDING PHYSICIAN ST. LUKE'S HOSPITAL; CHAIRMAN, SECTION ON PHARMACOLOGY AND THERAPEUTICS, AMERICAN MEDICAL ASSOCIATION, 1919.

Atropin.[2] This drug has such a decided action on certain secretions and certain motor functions of the body that it has for long years been assumed to have similar effects in the stomach. Yet clinical beliefs that have been supported by the leaders in medicine have so often been forced aside when the light of experiment has been turned upon them, that it behooves us to appraise carefully the value of such a drug as atropin in its application to the stomach.

1. *Secretion.* Observations on human subjects have been made by Crohn with the fractional method of gastric analysis. Some of his results were:

(*a*) *In Hyperacidity Cases with Normal Secretion Period.* One mg. ($\frac{1}{65}$ grain) of atropin sulphate administered to the patient hypodermically three-quarters of an hour after the meal, had little or no effect except that in the last one-half hour there was a rapid *rise* in acidity to 76 at a period when the control showed an acidity of 32. A similar experiment on another patient gave practically the same results. Doses by mouth sufficient to give signs of belladonna-poisoning (dry mouth, dilated pupil, etc.), raised the average acidity from 35 to 51.1. In all cases the motility was unaffected.

(*b*) *In Cases with Continuous Secretion.* In the control test a highly acid gastric juice persisted to the end of the experiment, six and three-quarter hours, though all the food had left the stomach at two and three-quarter hours. After the food had disappeared the acidity was higher than before, reaching 118 at four and one-half hours. The average total acidity was 89.

The next day with the same patient, all food having left the stomach at two and one-quarter hours, 1 mg. of atropin sulphate was given at this time hypodermically, and at one hour later the secretion had ceased. In the same patient fully atropinized by mouth for

[1] Presidential Address at the Twenty-second Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 9 and 10, 1919.

[2] Auer and Meltzer: Am. Jour. Physiol., 1906, xvii, 17.
Barclay, A. E.: Alimentary Tract, 1915, p. 17.
Crohn, B. B.: Am. Jour. Med. Sc., 1918, clv, 809.
Cushny, A. R.: Pharm. and Therap., 1915, p. 323.
Ginsburg and Tumpowsky: Arch. Int. Med., 1918, xxii, 553.
Ochsenius, K.: 1915.
Rehfuss, M. E.: Tr. Am. Gastro-Enterol. Assn., 1918, p. 25.
Smith, Maurice I.: Am. Jour. Physiol., 1918, xlvi, 232.
Zunz and Tysebaert: Jour. Pharm. and Exp. Therap., 1916, viii, 325.

three days the stomach was free from food at three hours and the secretion ceased at three and one-half hours. The average total acidity was 60 as compared with an average of 89 in the control, but in this case the averaging of acidities does not make a valid comparison, because in the control the highest acidity was reached during the period of continued secretion, *i. e.*, after digestion was finished, a period in which there was no secretion at all after atropin. In this case exploratory laparotomy had shown no lesion.

In a second case the secretion was still continuous at five and three-quarter hours when the experiment was stopped. The average total acidity had *risen* from 85.3 to 94, the motility being unaffected. Then tincture of belladonna, 1 c.c. four times a day, was given by mouth for three days, when poisonous symptoms appeared. In a test at this time the secretion ceased at three hours, but the average acidity increased from 85.3 to 104.5.

We find then failure of atropin to lessen digestive secretion, and in continuous secretion cases a failure to act except after the digestive period. Then it had an effect only if given by hypodermic in maximum doses, or if previously given by mouth to the stage of poisoning. It actually increased the acidity of the digestive secretion and showed an inhibitory effect only on the abnormal continued post-digestive secretion.

In regard to the psychic secretion I have only the report of Rehfuss. In the early morning each of a number of men with a fractional tube in his mouth was set in front of a beefsteak and compelled to cook it though not allowed to eat it. The stomach secretion, withdrawn at intervals, ceased at sixty to eighty minutes and ran as high a total as 240 c.c., with average acidity of 97.2. In large doses by hypodermic atropin cut down the acidity and the amount of secretion, but never caused complete disappearance of the secretion. It is possible that the drying effect of atropin in the nose, mouth and throat and the sensory effect of blunting the sense of smell may have been important in the result.

2. *Motor Functions.* From a therapeutic point of view the only desired action of atropin on the motor functions is to overcome tetanic spasm at the cardia, at the pylorus and at the site of an hour-glass contraction.

Working with strips from the antrum, pre-antrum, body and fundus of the stomachs of rabbits, cats and dogs, Smith found that solutions of atropin sulphate 1 in 1,000,000 and 1 in 100,000 invariably produced relaxation, whether the strips were from the longitudinal, the circular or the oblique muscles. He obtained the same effects on the pyloric and cardiac sphincters. Zunz and Tysebaert, working on the stomachs of dogs one-half hour after hypodermics of from 0.005 to 1 mg. per kilo, found the contractions weak and diminishing in strength, the effect in some cases persisting five to six hours. After 0.001 mg. per kilo the movements were normal,

though the tone rapidly fell. Auer and Meltzer have demonstrated that these effects are due to paralysis of the vagus terminals at Auerbach's plexus.

I have not worked with stomach strips, but in experiments done with Dr. C. C. Lieb, using strips of the longitudinal muscle of the small intestine of dogs, atropin in large amounts completely abolished the tetanic contraction or cramps brought out by physostigmin and restored the peristaltic waves, but not the normal tone waves. From the work of others it is established that the same action takes place in the stomach. Ginsburg and Tumpowsky, for example, found that hypodermics of $\frac{1}{80}$ to $\frac{1}{40}$ grain invariably in five to ten minutes inhibited the tetanic contraction produced by pilocarpin and physostigmin in the stomach and restored the normal peristalsis. The inhibition was sudden and decisive and persisted for hours. The same results were obtained in the isolated stomach.

This conquering of tetanic spasm by atropin in doses which permit the vagus and splanchnic nerves to continue their ordinary influence on peristalsis has led Cushny to surmise that these abnormal contractions, such as are seen in pylorospasm and colic, arise from some mechanism distinct from that which presides over ordinary peristalsis. This action on abnormal tetanic contractions is indeed *the only possible motor effect of therapeutic amounts of atropin.* It seems therefore essential to distinguish the two known motor effects, viz., that of abolishing abnormal spasmodic contractions and that of abolishing the tone of the whole stomach wall. Only the former is possible or desirable therapeutically, and in all probability it is not accomplished by paralysis of the vagus endings.

Clinically and in roentgen-ray work, atropin has been much employed to overcome abnormal tetanic contractions. On cardiospasm, which it is agreed is not a true spasm, the drug has little or no effect. In röentgenology it is quite generally employed to overcome pylorospasm and the spasm of hour-glass contraction. From fluoroscopic observations, A. E. Barclay reported that after the dose of atropin the spasm often let up quite suddenly, but in some cases the drug was without effect. From a number of roentgenologists I have learned that quite frequently even large doses are without effect on pylorospasm. These men do not use small doses, but are accustomed to the employment of 1 to 1.2 mg. ($\frac{1}{65}$ to $\frac{1}{50}$ grain) of the drug, and that hypodermically, or some of them attempt to atropinize by two or three days' dosage. Within a few weeks I have had a case operated upon for cholelithiasis in which the roentgenologist, finding an hour-glass stomach that did not change after a hypodermic of 1 mg. of atropin sulphate, insisted on a diagnosis of ulcer with cicatricial contraction. But at the operation there was no sign of either hour-glass or ulcer.

In Czerny's pediatric clinic, Ochsenius found that in infants

enormous doses were necessary to overcome pylorospasm. For instance, in one child, a month old, to permit proper feeding, he had to keep up intermittently for ten weeks an atropin dosage of 0.15 mg. ($\frac{1}{435}$ grain) five or six times a day, and in another, three weeks old, had to give the same dose eight times a day for a whole week. There is much evidence of the ineffectiveness in pylorospasm of any but large doses at any age and in adults of the ineffectiveness of any but hypodermic doses; even then the relaxation is frequently not obtained.

Summary. 1. *Acidity and Secretion.* 1. In the ordinary hyperacidity case with cessation of secretion at the usual time, atropin or belladonna in maximum doses, either by mouth or hypodermic, has no useful effect on acidity or secretion.

2. In cases with continuous secretion a maximum dose by hypodermic half an hour before the meal did not lessen the acidity or secretion of the digestive period, but resulted in a stoppage of the secretion in a reasonable time after the food had left the stomach. A similar maximum dose at the end of the digestive period stopped the secretion in one hour.

3. In cases with continuous secretion, repeated maximum doses of the tincture of belladonna by mouth for three days caused a pronounced increase in acidity during the digestive period, but a cessation of the secretion after the food had left the stomach.

4. The psychic secretion is lessened, an effect not sought in therapeutics.

5. The natural secretion of mucus is not affected.

We find then a complete failure of atropin to affect hyperacidity favorably and a failure to diminish secretion except in continuous secretion cases. In these cases it does not depress and may even increase acidity and secretion during the digestive period, and it checks the continuous secretion only when given by hypodermic in maximum doses or when previously given by mouth to the stage of poisoning.

II. *The Motor Functions.* 1. Atropin can exert two kinds of motor effects on the stomach: (*a*) the abolition of tone in the whole stomach wall including the orificial sphincters, by action on the vagus myoneural junctions, and (*b*) the abolition of abnormal spasmodic contractions, as in pylorospasm, this effect probably not being dependent upon any action on the vagus terminals.

2. The latter effect is the only desirable one in therapeutics. It is a possible effect in some of the cases only, and then only from maximum doses.

3. So far as I know the action of atropin on hunger contractions has not been studied.

Conclusions. 1. In hyperacidity cases atropin has no useful effects in any dosage.

2. In continuous hypersecretion cases it may check the secretion after the digestive period, but it does this in maximum doses only.

3. In pylorospasm it may be useful, but in maximum doses only.

4. In the doses usually employed it is wholly without effect on the secretory or the motor unction of the stomach.

PEPSIN.[3] By the U.S. Pharmacopœia test, with 1 in 3000 hydrochloric acid at 125.6° F. (52° C.), pepsin is required to digest 3000 times its own weight of coagulated egg albumen in two and one-half hours, *i. e.*, 1 grain of pepsin can digest at least $6\frac{1}{4}$ ounces. Prof. Gies, of Columbia, tells me that a specimen has been prepared 200 times as strong as this, *i. e.*, 1 grain can digest 600,000 times its weight. What a wonderful substance to have so little use in medicine! It is inactivated by hydrochloric acid above 0.5 per cent. strength (U. S. P.), 0.7 to 0.9 per cent. (Hamburger and Halpern), and by sodium chloride solution of 2.5 per cent. strength. It is not only inactivated but is destroyed by alkalies, for example, disodium phosphate in $\frac{1}{2}$ per cent. strength (Hamburger and Halpern), sodium hydroxide in 0.01 per cent. strength (Sollmann) and sodium bicarbonate and carbonate, magnesium carbonate and lime-water (Hamburger and Halpern), when in sufficient amounts to make a persistent alkaline reaction. In the light of this destruction one wonders how Abderhalden and Meyer were able to find active pepsin in all parts of the small intestine, and to suggest that this pepsin would be active in the digestion of protein wherever the intestinal contents should become acid.

In the stomach contents, Wiltrup found it absent or below normal in every one of a thousand cases of achylia gastrica. Hernando and Alday found it absent in 3 cases and present in only very small amounts in 16 out of 22 cases of gastric cancer and in normal or above normal amounts in 65 cases of hyperchlorhydria, 37 cases of gastric or duodenal ulcer and 85 cases of cicatricial stenosis of the pylorus.

It is evident then that the only possible cases for the use of pepsin in therapeutics would be those of subacidity and achylia, whether cancerous or not. Its need is doubtful, but since pepsin digests protein only when this has been changed to acid albumin, if used at all it should be accompanied by a sufficient quantity of hydrochloric acid.

Pepsin preparations regularly have a milk-coagulating power. Whether this is due to admixture of rennin or because pepsin and rennin are one and the same enzyme is a still unsettled question among physiological chemists.

RENNIN.[4] Rennin is not a digestant, but it has the power to coagulate from 5000 to 166,000 times its weight of milk in from one

[3] Hamburger, W. W., and Halpern, B.: Arch. Int. Med., 1916, xviii, 228.
Hernando, T., and Alday, T.: Siglo Med., Madrid, March, 1917.
Wiltrup, G.: Hospitalstidende, August, 1916.

[4] Harris: Jour. Anat. and Phys., 1894, xxix, 188.

to several minutes. The rennin curd uses up 13 per cent. more calcium phosphate than the curd from hydrochloric acid (Harris) and is less dense and more readily acted upon by pepsin.

The function of rennin in the gastric juice is therefore to retard milk in the stomach by changing it to a solid and to favor the digestion of its coagulable protein.

But in a medium strongly acid or more than slightly alkaline the rennin will not act. Therefore, on the one hand, in hyperacidity cases the curd formed is regularly the dense and comparatively indigestible acid curd and not that of rennin; and on the other the addition to milk of more than a very little lime-water or sodium bicarbonate, or as little as 2 grains of sodium citrate to each ounce will prevent the rennin coagulation, and will keep the milk in its liquid and less digestible form. In highly acid stomachs, however, it may take considerable alkali to prevent the undesirable acid coagulation of milk.

If we add rennin to milk just at the time of swallowing, may we not find this a useful remedy (1) in achylia cases with diarrhea, to coagulate the milk and so prevent its too rapid passage into the intestines, and (2) in hyperacidity cases to forestall the undesired acid coagulation?

Hydrochloric Acid.[5] The known functions of this acid in the normal animal are:

1. To favor protein digestion and the disintegration of connective tissue.
2. To induce closure of the cardia.
3. To establish a normal intermittence of opening and closure of the pylorus.
4. To serve as antiseptic.
5. To aid inversion of the disaccharides.
6. To form secretions to stimulate the production of pancreatic juice and bile.

That the absence of hydrochloric acid is quite compatible with

[5] Arny, H. V.: Practice of Pharmacy, 1918. Crohn, B. B.: Am. Jour. Med. Sc., 1918, clvi, 656.
Ginsburg, Tumpowsky and Hamburger: Jour. Am. Med. Assn., September 30, 1916.
Goiffon, R.: Arch. Mal. de l'Appar. Digest, 1918, ix, 262.
Horner, C. P.: Jour. Am. Med. Assn., December 8, 1917.
Jones, N. W.: Am. Jour. Med. Sc., 1918, clv, 335.
Joubert: Quoted by Goiffon.
Leo: Die Salzsäuretherapie auf Theoretische und Praktische Grundlage, Berlin, 1908.
Long, J. H.: On the Physiological Activity of Combined Hydrochloric Acid, Investigations of the Therapeutic Research Committee of the American Medical Association, 1915, vol. iv.
Marriott, W. McK., and Howland, John: Johns Hopkins Hosp. Bull., 1918, p. 284.
Rehfuss, M. E.: Jour. Am. Med. Assn., 1917, lxix, 1328.
Spencer, Meyer, Rehfuss and Hawk: Am. Jour. Physiol., 1916, xxxix, 459.
Stehle, R. L.: Jour. Biol. Chem., 1917, xxxi, 461.

fair health and the maintenance of nutrition is proved by the frequency with which the existence of achylia gastrica is discovered after only insignificant symptoms or no symptoms at all. I found achylia present in one girl, aged seventeen years, with complete lack of gastric symptoms, having tested her stomach merely because her grandmother and her mother had shown achylia. For hydrochloric acid as a remedy only one use can be suggested, viz., to replace a deficiency of acid in the gastric juice. Whether introduced acid can so serve is our question.

1. *Protein Digestion.* It is an established fact that for pepsin digestion of protein, acid is necessary. Therefore in an achylia case, if we are to have any digestion of protein in the stomach, we must supply hydrochloric acid as well as pepsin. Experiments done without pepsin regularly show a fair formation of acid albumin and thus give hope that the addition of pepsin may ensure at least some degree of gastric protein digestion.

Crohn, in fractional experiments on man in achylia cases, both simple and those of pernicious anemia, found that it was not possible to have a sustained acidity from mouth doses unless these were frequently repeated during the digestive period. To mention some of his experiments, in an *emptied fasting stomach* he placed 40 minims of diluted hydrochloric acid mixed with 100 c.c. of water. The immediate acidity was: Free 32, total 40. Successive specimens withdrawn at five-minute intervals showed rapidly diminishing acidity until at twenty-five minutes the titer was the same as before the acid had been given. When he administered 30 minims of diluted hydrochloric acid with an oatmeal test-breakfast the free and total acidities at fifteen minutes were 8 and 20 and at thirty minutes 12 and 18, but at forty-five minutes and thereafter had returned to 0 and 10 or thereabouts, the same as in the control experiment.

Then he administered repeated instead of single doses of the acid. Ten minims of the diluted acid every half hour during digestion gave a mild but definite rise in acidity which was sustained for one and three-quarter hours, and 10 minims every quarter hour raised the average total acidity from 20 to 55. The emptying time was unchanged.

Leo, quoted by Crohn, gave achylia cases large doses of hydrochloric acid, equivalent to from 75 to 225 minims of U. S. P. diluted hydrochloric acid, and obtained increases in total acidity but rarely any free acid.

Spencer, Meyer, Rehfuss and Hawk introduced strongly acid solutions (0.542 and 0.4 per cent.), and found that the gastric contents had returned to normal at the end of one hour. This they attributed to a rapid emptying due to the acid and a progressive neutralization of the excess of acid.

Rehfuss found that 10 or 15 minims of hydrochloric acid, properly

diluted, made no detectable change in the gastric chemistry. However, with a constant supply of acid for two hours by a Murphy drip at the rate of 200 c.c. of 0.25 per cent. acid per hour, equivalent to 5 c.c. of diluted hydrochloric acid per hour, the curve of secretion rose to 33 per cent. of normal, though there was at no time any free acid.

All these findings indicate that if we can only give enough hydrochloric acid by mouth, we can at least hope to change our albumin to acid albumin and thus prepare it for pepsin digestion. But acid alone is practically useless for the purpose of digestion, and to judge of its merits as a remedy, it must have all the factors for its action. In other words, we must administer pepsin with it. Moreover, the products of the action of pepsin and hydrochloric acid on protein are themselves capable of exerting a strongly stimulating effect on secretion.

Sippey makes a calculation that for the adult allowance of 100 gm. of protein a day it would require 700 minims of diluted hydrochloric acid for full gastric digestion, and that on account of the sensitiveness of the mouth and throat to acid it would be impossible to swallow this amount. However, there is never, even in normal cases, full protein digestion in the stomach. Moreover, some proteins require less acid than others for digestion, *e. g.*, Hawk states that the best strength for the digestion of fibrin is 0.08 to 0.1 per cent., while the best for coagulated egg-white is 0.25 per cent. Joubert found in achylia cases that on giving hydrochloric acid at the same time as raw meat, connective tissue still appeared in the stools. From strengths of 30 to 40 minims in 100 c.c. of water Crohn noted the development of considerable mucus, presumably from some local irritant action.

2. *The Emptying Time of the Stomach.* That in achylia gastrica it is not infrequent to have a very rapid emptying time is well known. In 11 cases of pernicious anemia, C. P. Horner found that 6 had emptied at one hour and in only 1 was there food at the two-hour period. N. W. Jones in a study of achylia concluded that in a broadly built non-ptotic person achylia is usually associated with a too rapidly emptying stomach and in this class diarrhea is prone to occur; whereas in ptotic types the ptosis and atony prolong the emptying time even up to seven hours or more, and in this class constipation is the rule.

There is considerable clinical evidence that in a fair number of achylic diarrheas, hydrochloric acid is a successful remedy. May not this be due to the restoration of the normal pyloric closure through the acid reflex and the consequent retardation of the food in the stomach? This, it is to be remembered, is a desired effect only in those cases with rapid emptying and diarrhea, and it is to be avoided if possible in those cases with flatulence or constipation. Crohn found the emptying time normal after doses of acid, but he

does not state that any of his cases were of the diarrheal type. Goiffon states that 1.5 to 3 gm. of hydrochloric acid a day may act to cause pyloric closure and so retard the food in the stomach. Jones's experience with the use of acid tallies with that of the author. He says "many are symptomatically relieved by its use, while others experience increased sourness and stomach irritation."

It has been stated that in some achylia cases the diarrhea may be checked by the administration of pancreatin. May not part of the value of hydrochloric acid lie in its power to enhance the pancreatic secretion through the formation of secretin, and thus to ensure more thorough digestion of proteins in the intestines? For though achylia gastrica is not ordinarily accompanied by pancreatic achylia, yet for certainty of digestion the rapidly passed food may require abnormal amounts of the pancreatic ferments.

3. *The Antiseptic Action.* In an achylia case it is quite common to find pronounced intestinal putrefaction. In both diarrhea and constipation cases this may be attributed, in part at least, to the failure of the achlorhydric contents to arrest the development of gas-forming organisms and to destroy the sundry proteolytic and pathogenic germs, thus permitting their passage into the upper intestine. In diarrhea cases intestinal putrefaction might also be accounted for by the fact that the ferments have too short a time in which to break down the protein before it reaches the usual region of abundant germ life in the intestine, and so the protein furnishes pabulum for the bacteria of the colon.

4. *The Effect on Pancreatic Secretion and Bile.* It is a well-established fact that, in the normal case, the hydrochloric acid of the stomach is an important factor in the production of secretin which stimulates the secretion of pancreatic juice and bile. What takes the place of hydrochloric acid in the achylia case, which does not lack pancreatic ferment, has not been determined; but if, from introduced acid, free hydrochloric acid or combined acid, which is really a loosely combined protein salt, can be passed into the duodenum even for a few moments, may not this result in the formation in the normal manner of ample secretin, and so provide the normal stimulus for the production of pancreatic juice and bile?

Summary. In achylia cases, from experiments based on the introduction of hydrochloric acid alone, without its natural congener pepsin, it is evident that with single doses of swallowable strength the acid titer of the stomach contents may be distinctly raised even to the normal. The results that might be expected from this are: (1) Successful protein digestion in the stomach when sufficient pepsin is also introduced; (2) slowing of the emptying time of the stomach by reëstablishment of the pyloric closure reflex; (3) restoration of the normal antiseptic action in the stomach; (4) the proper formation of secretins; (5) normal liquefaction of the stomach contents by the added fluid.

Possible drawbacks to its use are: The establishment of pyloric closure in an already slowly emptying stomach, the production of gastric irritation, and the development of a mineral acidosis from its daily use over long periods of time. That it can produce *acidosis* has been demonstrated in dogs by a number of observers, and recently in man by Marriott and Howland. They gave 500 c.c. of decinormal hydrochloric acid in one day to each of four normal men, who ate their usual diet. This amount would represent 273 minims of diluted hydrochloric acid, a very large amount. On that day there was a distinct increase in the ammonia coefficient in the urine and at the same time an increase in the titratable acid in about the same proportion. Thus in a single day from swallowable amounts in man ammonia was deflected from the usual course of nitrogenous metabolism and a certain degree of acidosis was produced.

Stehle administered hydrochloric acid to dogs by mouth and found an increased excretion of sodium, potassium, calcium and magnesium. In the case of sodium and potassium, however, a subsequent compensatory retention took place. It has been figured that among the other effects there is a loss of calcium from the bones.

It is of interest that Ginsburg, Tumpowsky and Hamburger found hydrochloric acid in 0.5 per cent. concentration to be without effect on the hunger contractions.

Conclusions. 1. In cases of achylia gastrica, whether or not accompanying pernicious anemia, a deficiency of acid may be partially overcome by hydrochloric acid medication.

2. For digestive purposes hydrochloric acid should always be accompanied by pepsin.

3. In the achylias with diarrhea, acid promises a more noticeable result than in the achylias without diarrhea.

4. When acid produces sourness and stomach irritation its use should not be continued.

5. To avoid acidosis alkalies should be given during the same period, though not at the same time as the acid, the amount required being judged by the effect on the urine reaction.

To avoid the trouble of frequent medication in cases of achylia gastrica I have found it a good plan to have the patient take at the main meal most of the putrefactive protein of the day, such as eggs and flesh foods, the allowance of which is small in these cases, and have the acid and pepsin taken with this meal only. For practical reasons liquid medicine cannot be taken for any length of time after the meal, but doses of 20 or 30 minims of diluted hydrochloric acid and a few grains of pepsin in a full glass of water may be taken with the meal and frequently at half and even one hour later.

THE SOLID HYDROCHLORIC ACID PREPARATIONS. In solid form there are marketed certain drugs purporting to contain hydrochloric acid available for digestive purposes. The best known are *oxyntin,*

a protein compound of hydrochloric acid, and *acidol,* which is chemically betaine hydrochloride. In a careful research under the auspices of the American Medical Association, J. H. Long found that acidol dissociates in an aqueous medium and supplies hydrochloric acid, but that oxyntin holds scarcely enough acid for the digestion of its own protein and cannot therefore supply any for other digestion.

Nitrohydrochloric Acid. Nitrohydrochloric acid has frequently been employed by the older physicians. It is made by mixing hydrochloric and nitric acids, a violent reaction taking place, and the acids being split up to form nitrosyl chlorides and chlorin. There is a slight excess of hydrochloric acid, so that nitrohydrochloric acid of the U. S. Pharmacopœia is a liquid containing free hydrochloric acid, free chlorine and nitrosyl chlorides (Arny). It hardly seems worthy of a place in the materia medica.

Bitters.[6] In Carlson's tests on a young man in good health, who had an esophageal obstruction and a permanent gastric fistula for feeding purposes, bitters were administered either by stomach fifteen to thirty minutes before meals or by mouth ten minutes before the meal. The patient was in the habit of taking his food by mouth, chewing it and then placing it in the stomach through the fistula. The bitters were the tinctures of gentian, quassia, calumba, humulus and condurango and the elixir of iron, quinin and strychnin. The tests numbered 50 with bitters taken into the mouth, 35 with bitters placed in the stomach and 50 without bitters for control.

When the bitters were taken by mouth they could not be retained long because of the salivation induced and had to be expectorated. Their effect on the appetite of this young man in good health was too slight to be of moment, though it was noted that at the evening boarding house meal, which was never relished, the effect of the bitters was to make an already undesired meal still more undesirable.

When the bitters were placed directly in the stomach small amounts were found to have no influence on the quantity of the psychic secretion or on the acidity or pepsin concentration of the gastric juice. When large amounts were used Carlson's results agreed with those of other observers that their action in the stomach itself was rather to retard than to increase the activity of gastric digestion.

With tests on healthy dogs Carlson further came to the conclusion that bitters acting either in the mouth or in the stomach have no effect on the secretion of the gastric juice.

In another series of experiments Carlson and his colleagues showed that bitters acting in the stomach alone have no appreciable influence on the hunger mechanism as distinguished from appetite,

[6] Carlson, A. J.: The Control of Hunger in Health and Disease, 1916.
Hoppe: 1905, quoted by Moorhead.
Moorhead, L. D.: Jour. Pharm. and Exp. Therap., December, 1915, p. 577.

and that when taken by mouth in the usual way they inhibit gastric tonus and hunger contractions in direct proportion to the intensity and duration of stimulation of the nerve-endings in the mouth. In other words, *in normal people*, so far as they influence the hunger mechanism directly the bitters cause inhibition or depression of hunger.

Arguing from these experiments Carlson takes the ground that the whole value of bitters in medicine is mental and that they are in the same class as an inert but widely advertised patent medicine. He thinks that their continued use depends on two beliefs of the patient, namely, that they will promote appetite, and that anything with a strong and bad taste is strong medicine and therefore good medicine.

On the other hand, Hoppe noted that in a sick dog the use of bitters was followed by an increase in the quantity and acidity of the gastric juice, and Moorhead found that while in normal dogs bitters had no influence on appetite and no influence on secretion or a depression of it; nevertheless, in dogs made cachectic by daily bleedings to produce a chronic anemia they caused a distinct and significant increase in both appetite and secretion. Placed in the stomach without touching the mouth they had no appreciable influence. Barisoff gave tincture of gentian to a dog with the end of the severed esophagus opening outside, so that substances swallowed did not reach the stomach. He followed this with a meal, and in 6 tests without the bitters and 6 tests with found that after the bitters the average amount of gastric juice increased 30 per cent. If he gave the bitters as long as twenty minutes before the meal this effect was not obtained. An excess of bitters checked the secretion.

I myself have noted in many cases of achylia gastrica that bitters have the power to create or increase appetite, though having no effect on the gastric secretion. And I would register my opinion that in many persons with subnormal nutrition, especially in those recovering from an acute illness, bitters have a real value in promoting appetite, and that this action is not dependent on the patient's belief in the efficacy of the drug.

Conclusions. A bitter is useful as an appetizer for those with subnormal nutrition, as in convalescence from acute illness, provided that it is taken not more than five to ten minutes before the time for eating. It acts in achylia gastrica as well as in cases with gastric secretion. In subacidity it promotes the secretion of gastric juice. It should be administered in just sufficient dose to give a strong bitter taste and not in amounts large enough to have a depressant action in the stomach. If the patient is in a state of normal nutrition, but psychically disturbed about eating, it will be useless. If the appetite is already normal the bitter may not only fail to increase appetite but may even lessen it. If the stomach and bowels are deranged bitters may nauseate. The effect on appetite is solely

the local one on the taste buds, therefore it cannot be obtained if the bitters are hidden in capsules or coated pills.

CERIUM:[7] The oxalate, which is the one salt employed, was studied by Baehr and Wessler. They found that it is non-poisonous to dogs even in doses of 50 grams, and that its action is mechanical as a protective to the gastric mucous membrane. Administered in advance it would check the vomiting from a local stomach irritant, such as ipecac, but had no influence on the vomiting from a central emetic, such as apomorphine. They state that the drug is useless in the small doses usually administered and recommend that it be given in doses at least as large as those of the bismuth salts.

BISMUTH.[8] The bismuth salts in common use are the subcarbonate, the subnitrate and the subgallate. The subnitrate is crystalline, and because of this fact probably less bland than the others, which are amorphous. Contrary to the general belief they are all without astringency, that is to say, they do not cause shrinkage of tissues with which they come in contact.

Being basic salts they have the power to take up acid. Theoretically, of *bismuth subnitrate* 1 gram will neutralize 2 c.c. of diluted hydrochloric acid, or the acid of at least 40 c.c. of gastric juice, with the formation of bismuth nitrohydrochloride. But the change takes place very slowly and Böckman has demonstrated that in such acid concentrations as are found in the stomach the subnitrate possesses but little acid neutralizing power. Of *bismuth subcarbonate,* 1 gram will neutralize 4 c.c. of diluted hydrochloric acid or the acid of at least 80 c.c. of gastric juice, with the formation of bismuth chloride. It does not change to bismuth oxychloride as so frequently stated, for this basic salt cannot form in an acid medium. Bismuth subcarbonate changes somewhat more rapidly than the subnitrate, but not rapidly enough to justify attributing any important part of its action to its acid neutralizing power.

In a study of test-meals with the addition of bismuth subcarbonate, and fractionally extracted every fifteen minutes, Crohn reported that 2-gram doses given directly after the meal caused a diminution in acidity without any compensatory increase (as found after alkalies) in the acid secreted. According to a published chart he administered the salt half an hour after the meal, and up to the one and one-half hour period found the acidity slightly higher than in the control. But at one and three-quarters hours he got an acidity of 40 as compared with 70 for the control, and at two and one-quarter hours 50 as compared with 68. There was a slight retardation in the empyting time. In a duplicate experiment with a slightly greater dose the acidity was depressed from 56.8 to 45.2

[7] Baehr, G., and Wessler, H.: Arch. Int. Med., 1908, ii, 517.
[8] Böckman: Arch. Exp. Path. und Pharm., 1916, lxxx, 140.
Böhme, G.: München. med. Wchnschr., 1908, lv, 89.
Crohn, B. B.: AM. JOUR. MED. SC., 1918, clv, 808.

without delay in emptying or any evidence of the secondary rise in acidity which regularly follows the administration during the digestive period of the alkalies and alkaline earths.

Some years ago, in a number of instances, I administered doses of 2 grams of bismuth subnitrate just before or just after the test-breakfast, and though at the end of the hour the stomach contents usually showed a lessened acidity, and also a lessened secretion as determined by the Matthieu-Rémond method, there were a few cases in which the acidity was unchanged. Unfortunately, the protocols and the case records of these experiments were destroyed, so that I am not able to figure a reason why the bismuth should fail in these instances. In every case it was noticed that at the end of the test-breakfast hour the bismuth was uniformly mixed with the extracted stomach contents, and that it had changed from a heavy powder to a flocculent substance that settled slowly with the food. On two occasions I administered to dogs with their food, doses of 2 grams and 8 grams respectively of bismuth subnitrate colored red with carmin, and on removing the stomach and intestines three and seven hours later found the colored bismuth in this same flocculent and comparatively light state, partly mixed with the food residues, but mostly coating very uniformly the whole mucous membrane. In the dog killed at three hours it coated the stomach and small intestines throughout, except the first three or four inches of the duodenum. In the dog killed at seven hours it coated the whole jejunum and ileum. The coating stopped short at the ileocecal valve and there was no macroscopic evidence of bismuth in the colon.

Crohn's results with bismuth subcarbonate and mine with bismuth subnitrate would seem to be of the same nature, and would suggest that the action of either salt is not antacid but rather protective by coating the mucous menbrane. Their power to spread over a large surface of membrane is almost phenomenal. Crohn's work establishes the fact that while the bismuth salts affect the secretions they do not essentially change the motility. By their protective action these bismuth salts would seem to have a value quite equal to that of cerium oxalate in preventing vomiting from local stomach irritants, such as ipecac.

Toxicology. By mouth the bismuth salts are not ordinarily poisonous, though Kohn reported the development of stomatitis and other manifestations of metallic poisoning from doses of 0.3 gm. (5 grains) given four times a day (length of time not stated). But poisoning from the use of a bismuth paste in the treatment of sinuses is not uncommon. One fatality resulted from less than 10 grams of bismuth subnitrate mixed with vaselin. Therefore, it may be conceived as possible that if the bismuth salt given by mouth should be retained on a raw area such as an ulcer, metallic poisoning may occur. As demonstrated by the roentgen rays such retention is unusual, but at our last meeting Jacob Kaufmann mentioned a case

of hematemesis to which Naunyn had given 25 grams of bismuth subnitrate, and in which at the postmortem von Recklinghausen took out of the crater of the ulcer 20 of the 25 grams of bismuth.

The symptoms have the characteristics of poisoning by the heavy metals, viz., stomatitis, salivation, a violet, blue-gray or blackish line on the gums, nausea, vomiting, diarrhea and prostration.

After bismuth subnitrate, but no other bismuth salt, another form of poisoning has occurred, namely, nitrite poisoning, this being due to the formation of nitrous acid. Most of these cases have resulted from the ingestion of large amounts of bismuth subnitrate for roentgen-ray work; but there are a few that have occurred from the medicinal use of the salt. Böhme, for example, reported that after giving an eighteen months marasmic infant several grams by mouth and two days later a similar dose by rectum, the child three hours after the last dose suddenly developed abdominal pain, diarrhea, cyanosis, and dyspnea, and died in half an hour. The blood and pericardial fluid gave tests for nitrous acid, and the blood for methemoglobin. Böhme found that when he mixed bismuth subnitrate with feces, nitrous acid was formed, and that when he placed this mixture in a rabbit's intestine, the urine showed nitrites. In one fatal case E. Meyer demonstrated nitrites in the urine, blood and pericardial fluid.

Silver Nitrate. Before leaving the subject of drugs I wish to put on record a case of argyria that I have just found on my service, with a universal metallic slaty look to the skin, which came on after taking only $\frac{1}{4}$ grain of silver nitrate three times a day for two months.

I also this year had an autopsy on a similar case of argyria, in which the viscera were much discolored with silver deposits. This resulted from the application only once daily of a caustic silver stick to the mouth of a fistula. The period of application I do not know. This may point a moral for men who use silver nitrate in gastroenterology.

A ROENTGEN RAY SIGN OF PERINEPHRITIC ABSCESS.[1]

By M. H. Fussell, M.D.,

and

H. K. Pancoast, M.D.,

Philadelphia

During the study of Case II in this report a curious fluoroscopic finding was observed which directly led to a diagnsois of perinephritic abscess, and which was confirmed by operation. The same

[1] Read before the Association of American Physicians, Atlantic City, N. J., June 18, 1919.